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Informed Opinion

Fourteen Fallacies About Patient Package Inserts

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EDITOR'S NOTE: *FDA's patient package insert program was stopped in the wake of President Reagan's executive order requiring reconsideration of regulations that might cost at least $100 million, increase product costs or adversely affect competition.*

WHEN I moved to Washington in October 1979 to become Commissioner of the Food and Drug Administration (FDA), I resolved to enter my new responsibilities with an open mind, setting aside my prejudices so that I could more easily separate fact from fiction. I found this exercise quite useful. Many of the perceptions I had of Washington and of FDA were quickly altered by the reality I saw before me. What I learned is that accurate information, even in a community that thrives on media coverage, is at a premium, that it is often necessary to focus afresh on issues.

As Commissioner, the single issue that occupied more of my personal time was patient package inserts or PPI's. Because of my background, reporters and health professionals at every opportunity asked me what I was going to do about the PPI rule that FDA had proposed just before I came to Washington. In the first speeches I delivered, I made it clear what my position was:

- that I believed strongly in patient information;
- that patient package inserts were not necessarily the only way to provide such information, but present knowledge seemed to indicate they were;
- that I would keep an open mind about patient package inserts, but that I believed we needed to proceed to see how they work in a real-world situation, and
- that while this pilot program was going on, we still needed to explore alternatives.

You can imagine my surprise when, in midsummer of 1980, nine months after I arrived at the agency and after I had repeatedly expressed my views on patient package inserts, I still continually was asked, "How do you *really* feel about PPI's?" It became obvious that some people just were not listening, or perhaps did not believe, or did not want to believe, what they were hearing. In any event, on September 12, 1980, in a notice published in the federal government's paper of record, the *Federal Register,* FDA spelled out precisely the pilot program .I had been advocating. Patricia Roberts Harris, the Secretary of Health and Human Services, had such a personal interest in the program that she decided to announce it personally at a press conference. I met with representatives of health professional groups right after the press conference to answer questions and explain the program.

The response to our program took essentially three forms. Some believed that FDA was moving too slowly, that we should have proceeded with a massive PPI program at once. Others welcomed our initiative and believed the program had just the right balance of innovation and caution. Still others expressed skepticism about the program or rejected it out of hand.

The key to gaining support for the program, I learned, was simple: explain the reasoning behind it and why we thought it the best direction to take. I have found that people who understood

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what we were doing, tended to support it; those who did not understand it, tended to oppose it.

With this in mind, then, I have compiled 14 fallacies about patient package inserts and our proposed program. These fallacies have been distilled from my many conversations with consumers and health professionals about the PPI program.

I ask the readers of this article not necessarily to agree with me but to take a lesson from my experience with Washington and FDA: approach the subject with an open mind and set aside preconceptions. I believe that a clear understanding of the PPI program developed by FDA will lead to support for the concept from most of my colleagues in the health professions.

Fallacy Number One: There is no precedent for this kind of requirement. Actually, the first patient package insert was required by FDA in 1968, when it was recognized, at least implicitly, that some drugs could not be used properly unless certain information was conveyed to patients as well as to prescribers or dispensers. Thus, in June 1968, FDA required that each isoproterenol inhalation drug dispensed to a patient bear a two-sentence warning on the container advising of an association between repeated and excessive use and severe paradoxical bronchoconstriction. FDA required the warning because inappropriate use by patients was actually causing the condition the drug was intended to treat.

Other patient package information was required by FDA as the need emerged, particularly for drugs for which patient choice should be a factor in the prescribing decision. Thus, in June 1970, FDA required that patient information be dispensed with oral contraceptives. In July 1977 FDA required patient information for estrogens. In 1978, when new information became available about orally taken contraceptives, labeling for patients was revised to require more detail. Later, FDA established patient labeling requirements for intrauterine devices (IUD's) and for progestational drug products. Thus, a series of precedents for patient package information date back a dozen years.

Fallacy Number Two: FDA does not have legal authority to require patient package inserts. One test of FDA's legal authority to require PPI's resulted from a suit filed in 1977 against FDA's estrogen patient package insert regulation by the Pharmaceutical Manufacturers Association, the American College of Obstetricians and Gynecologists, and others. In February 1980 the US District Court for the District of Delaware upheld FDA's authority to issue the estrogen PPI requirement under the drug misbranding section of the Federal Food, Drug, and Cosmetic Act. Among other things, the court also found that the requirement did not interfere with any constitutionally protected rights of physicians to practice medicine. This decision has recently been affirmed by the US Court of Appeals for the Third Circuit.

TABLE 1.—*Results of FDA Review of Patient Noncompliance Rates From Studies Completed After 1969*

Drugs	No. of Studies	Percent Noncompliance		
		Range	Mean	Median
Cardiac	3[1-3]	20-45	33	34
Antihypertensive	5[4-8]	24-83	43	33
Penicillin	8[9-16]	11-95	45	38
Other antibiotic	5[17-21]	37-71	52	50
Antituberculosis	4[22-25]	28-53	42	43
Antipsychotic	8[26-33]	19-63	42	48
Multiple drugs	11[34-44]	25-80	60	43
Miscellaneous	6[35-40]	28-89	52	49

Fallacy Number Three: Patients don't need such information. Unfortunately there is abundant evidence showing widespread failure by patients to use drugs properly. Patients most frequently misuse prescription drugs by failing to adhere to the prescribed regimen, such as improperly spacing doses, failing to take the drug for the time necessary for adequate treatment, skipping doses or taking extra doses. Researchers have estimated the extent of patient noncompliance at 30 percent to 80 percent. FDA's own patient prescription drug labeling project reviewed patient noncompliance rates from studies completed after 1969. Each study reviewed by FDA included at least 40 patients. The results of that review are presented in Table 1.

Fallacy Number Four: Patients don't want the information. Interest in patient labeling has been expressed most forcibly by consumer activists. But a number of surveys indicate that consumer advocates accurately reflect broad public support for patient labeling.

For example, a 1973 nationwide survey sponsored by FDA showed that 49 percent of the respondents wanted additional information in nontechnical language dispensed with the products.[41] Similar findings were made by independent researchers who found that of 828 students and outpatients studied, 82 percent wanted to know more about prescription drugs than simple direc-

tions for use, specifically information about side effects and risks from overuse or underuse of a prescribed drug.[42]

In 1975 FDA sponsored a nationwide survey of 1,720 users of orally taken contraceptives. They were asked if they would like to receive patient labeling with other prescription drug products. Of the respondents, 93 percent believed it to be important to provide patient labeling for antibiotics, and 97 percent believed it important for tranquilizers.[43]

Results of a 1978 survey supported these findings, with 64 percent of 2,002 adults surveyed stating that they believed it important for printed labeling to be provided with prescription drugs. Only 33 percent stated that current practices seemed adequate. This two-to-one preference for patient labeling was consistent across all age, sex and educational subgroups.[44]

In 1980 I took my own informal survey through a unique two-way television hookup in Columbus, Ohio, known as QUBE. Consumers who responded to a series of questions clearly supported more information about prescription drugs and indicated a willingness to pay for it.

Fallacy Number Five: FDA was "steamrolling" the PPI requirement through without adequate study, research or opportunity for criticism. FDA leaned over backwards to assure that adequate study was conducted and all concerned parties given an opportunity to voice opinions against as well as for the PPI program. Following the patient labeling requirement for oral contraceptives in 1970, FDA began evaluating the usefulness of patient labeling for prescription drug products generally and studied ways to present the information most effectively. In line with suggestions made by FDA's National Food and Drug Advisory Committee, FDA began a patient prescription drug labeling project in 1974 to investigate whether patient labeling efforts should be expanded to a variety of prescription drug products. After this project began, FDA discussed patient labeling issues with all interested and potentially affected persons and groups, reviewed scientific literature about the information needs of patients, carried out research projects to evaluate existing and model patient labeling, and reviewed existing methods for communicating drug information to patients.

For example, between September 1974 and June 1975, FDA officials met individually with nine organizations representing physicians, pharmacists and the pharmaceutical industry; and, in July 1975, officials met with consumer representatives to discuss the general concept of patient labeling. These meetings were highly productive, identifying such major concerns as the criteria for choosing candidates for patient labeling, the possibility that patient labeling would interfere in the patient/physician relationship, the problems patient labeling might pose to pharmacists, consumer support for patient labeling, liability issues, the problems of conveying patient information in nontechnical language, information that should be included in patient labeling, the need for physician discretion to withhold labeling in certain instances, and logistical problems that might be created by storage and distribution of the inserts.

After FDA was petitioned in 1975 by a consortium of consumer organizations that favored patient labeling, the agency published a notice in the *Federal Register* soliciting comment. FDA received more than a thousand comments in response to this notice, all of which were carefully evaluated. In May and June 1976 FDA hosted four meetings at which consumer advocates and FDA officials met with representatives from the pharmaceutical industry, medical and pharmacy associations, and allied health professions to debate the issues raised by the consumer petition.

In 1976 FDA also invited the Drug Information Association, an independent nonprofit professional group interested in drug information, to arrange a symposium on patient labeling for prescription drug products at which a diversity of views could be presented. This symposium, held in November of 1976, was also cosponsored by the American Medical Association and the Pharmaceutical Manufacturers Association. More than 700 health professionals, consumers and information media representatives attended the symposium, the proceedings of which were published in January 1977 as a special supplement to Volume II of the *Drug Information Journal.*

FDA continued to solicit public comment on patient labeling, as exemplified by its having sponsored a two-day conference on the content and format of patient labeling. In February 1979, the Institute of Medicine of the National Academy of Sciences, under contract to FDA, sponsored a public hearing to solicit comments on how patient labeling should be objectively evaluated, once it is used on a widespread basis.

In addition, to stimulate comment on the proposal to require PPI's for certain drugs, FDA an-

nounced in August 1979 that three public hearings on the proposal would be held—in Chicago, Los Angeles and Washington, DC, respectively, on September 10, 12 and 14, 1979. The agency received some 1,500 comments from trade associations and individual firms involved in the manufacture and distribution of prescription drug products; from organizations of health care professionals and individual physicians, pharmacists, and members of other health care professions; from organized consumer groups and individual consumers, and from others.

A summary of the substantive comments on the proposal and FDA's responses appear in the preamble to the regulation published on September 12, 1980. A transcript of the public hearings is available for study in the FDA Hearing Clerk's office.

Finally, what FDA established in the PPI regulations it issued in September 1980 is a three-year pilot program for PPI's to be used to evaluate all the issues surrounding PPI's—including content, format, method of distribution and effectiveness—based on the experience gained with the ten drugs or drug classes for which PPI's would be required. In sum, I can think of no other FDA activity that has been more thoroughly studied than PPI's.

Fallacy Number Six: Patient labeling would have a detrimental psychological effect on patients. This is a concern that FDA has taken quite seriously. The agency has studied the literature on the effects of written information and found that it does not sustain this objection to patient labeling. Studies that have examined the rate of patient-reported side effects have found no difference between patients who received written information and patients who did not. One study did show that patients who received information were more willing to *report* side effects than patients who did not receive this information.[48]

In addition, an FDA-sponsored study evaluated the effect of a patient labeling piece for the antihypertensive thiazide drugs.[49] The study involved 249 patients in whom mild essential hypertension had been newly diagnosed. Two thirds of the patients were assigned randomly to a group that received the patient labeling. The remainder were assigned to a group that did not receive it. Preliminary results do not suggest an increased incidence of adverse effects in the patients who received the labeling. They were, however, better informed about the drug product and less likely to attribute physical complaints to it.

Accordingly, current studies do not support the contention that patient labeling will have negative effects on patients' use of prescription drug products. As part of the pilot program, FDA would continue to gather and review data on the effects of patient labeling on prescription drug use and would, of course, take into account any new information or insights in developing its patient labeling program.

In those instances where the physician believes that a patient package insert should not be given to the patient, the regulation would permit the dispenser to withhold the insert except for certain enumerated drugs, such as estrogen, and where patients specifically request the insert.

Fallacy Number Seven: Patient labeling would reduce a drug's placebo effect. The placebo effect is, of course, complicated and poorly understood. Much of the effect appears to be due to the relationship between physician and patient. Because the patient receiving a PPI would possess more knowledge about what effects to expect from a particular drug, and because patient labeling may enhance patient-physician communications, information in PPI's about the effects of the drug may even increase the placebo effect of the drug product.

Fallacy Number Eight: PPI's would merely add to the counseling burden of physicians forced to reassure frightened patients. It was expected that in most cases the information conveyed in the PPI would merely restate and reemphasize the information that the physician has given the patient when the product was prescribed. In such a case, it should not alarm a patient any more than did the oral information, nor should it significantly increase the length or number of contacts between physicians and patients. Further, patient labeling might help patients ask clearer questions than they now ask, thereby aiding the physician to come more rapidly to a precise response. This is confirmed by an FDA survey that showed only 12 percent of oral contraceptives users who said they read the labeling also said that it raised questions that caused them to contact their physicians.[43] Many of these questions were related to effects not mentioned in the labeling but experienced by the patients, such as spotting, bleeding, breast soreness and weight gain. Moreover, added patient-physician contact is not necessarily an untoward result of patient labeling. It is quite likely to lead to a patient population that is better educated about drug therapy and, thus, more likely to

comply with physicans' drug therapy efforts. It seems logical that less complete information would lead to greater need to contact physicians than more complete information.

Fallacy Number Nine: A survey showed that people exposed to PPI's actually know less than those who are not exposed to them. There is no such survey. This misconception may have arisen from another, quite different survey, showing that people exposed to PPI's *plus* counseling knew more than people exposed to PPI's alone, a result we would certainly expect.

Fallacy Number Ten: PPI's would be required for all drugs. The regulation announced in September 1980 involved ten drugs or categories of drugs: the ampicillins, benzodiazepines, cimetidine, clofibrate, digoxin, methoxsalen, phenytoin, propoxyphene, thiazides and bendectin (which was recently substituted for one of the original ten, warfarin).

In selecting these drugs, FDA considered the following factors: whether precise use of the drug is essential in achieving its therapeutic effect, whether the drug is widely prescribed and used, whether the drug has the potential of causing significant adverse effects, whether there are likely to be severe problems if patients do not follow the dosage schedule and directions for use, and whether use of the drug is largely a matter of personal choice by patients.

Fallacy Number Eleven: Physicians would be unable to prescribe a drug for an indication not contained in the PPI. FDA recognized that prescription drug labeling, including both professional and patient package inserts, does not always contain the most current information available to practitioners about the proper use of a drug. Because advances in medical knowledge and practice inevitably precede formal changes in prescription drug labeling, good medical practice and patient welfare *require* that practitioners remain free to use prescription drugs according to their best knowledge and judgment. Nothing in the Federal Food, Drug and Cosmetic Act prohibits practitioners from prescribing a drug product for a particular patient for an indication not contained in its labeling, and the PPI regulation does not change this general rule. Moreover, the patient package insert required under the regulation might not need to identify all indications for which a drug product is legally marketed. The agency intends to include in some of its guideline patient package insert texts the following statement which would deal effectively with this issue: "This drug may be used for other conditions as determined by your doctor."

Fallacy Number Twelve: PPI's are a vehicle whereby the government could impose its views of proper drug prescribing practices. PPI's are no more such a vehicle than are professional package inserts, almost all of which are approved by FDA before they are put into use. Moreover, although FDA would prepare and provide guideline patient package inserts that manufacturers, distributors, and dispensers could use to comply with the regulations, those persons would be free to prepare their own patient package inserts in compliance with the regulations.

Fallacy Number Thirteen: The PPI Program was mandated regardless of consequences. The PPI program was consistent with recommendations made in August 1979 by the Institute of Medicine of the National Academy of Sciences. The Institute of Medicine called for a comprehensive study of patient package inserts, pointing out that experience with inserts has been positive and that the most pressing need is for more research and testing of PPI systems in actual use. As a consequence, the regulations for the ten PPI's were cast in terms of a pilot project for a three-year evaluation period during which FDA would study the actual costs, benefits and other effects of patient package inserts, as well as alternative patient information systems.

Fallacy Number Fourteen: The PPI program sought to alter, or would alter, the traditional patient-physician relationship. PPI's would not adversely affect the roles played by physicians, or pharmacists, in patient care. The purpose is not to interfere with physicians but rather to see to it that information is made available that a patient can use to carry out a physician's directions, information that many believe would help transform the position of a great number of patients from passive compliance to active cooperation with physicians in a prescribed course of therapy.

I hope my discussion of these 14 "fallacies" has helped bring the proposed FDA PPI program into better focus. It is not surprising that so many questions arose about a program that would directly affect as many patients and health professionals as the PPI program would.

Addendum

As this article goes to press, the Reagan Administration is preparing to go to the *Federal*

Register with an indefinite stay of the patient labeling regulations. It is their intent to reconsider the proposal and the final outcome is thus in some doubt. I continue to believe in the approach we developed, which would generate some answers as to the best way of educating patients about prescription drugs, and hope the new administration decides to continue the experiment.

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